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J. Vernikos, Ames Research Center, Moffett Field, California
M. F. Dallman, UCSF, San Francisco, CA
L. C. Keil and D. O'Hara, Ames Research Center, Moffett Field, California
V. A. Convertino, NASA Kennedy Space Center

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Ames Research Center
Moffett Field, California 94035-1000

Gender Differences in Endocrine Responses to Posture and 7 Days of 6° Head Down Bed Rest

J. VERNIKOS,* M. F. DALLMAN,** L. C. KEIL,* D. O'HARA,* and V.A. CONVERTINO†

Ames Research Center

Abstract

Endocrine regulation of fluids and electrolytes during seven days of 6° head down bed rest (HDBR) was compared in male (n = 8) and, for the first time, female (n = 8) volunteers. The subjects' responses to quiet standing for 2 hr before and after HDBR were also tested. In both sexes, diuresis and natriuresis were evident during the first 2-3 days of HDBR, resulting in a marked increase in the urinary Na/K ratio and significant Na retention on reambulation. After the first day of HDBR, plasma renin activity (PRA) was increased relative to aldosterone, plasma volume was decreased and the renal response to aldosterone appeared to be appropriate. Circulating levels of arginine vasopressin (AVP), cortisol and ACTH were unchanged during HDBR. Plasma testosterone decreased slightly on day 2 of HDBR in males. The ratio of AM ACTH to cortisol was lower in females than in males because ACTH was lower in females. Urinary cortisol increased and remained elevated throughout the HDBR in males only. There were no gender differences in the responses to 7 day HDBR, except those in the pituitary-adrenal system; those differences appeared unrelated to the postural change. The provocative cardiovascular test of quiet standing before and after bed rest revealed both sex differences and effects of HDBR. There were significant sex differences in cardiovascular responses to standing, before and after HDBR. Females had greater PRA and aldosterone responses to standing before bedrest and larger aldosterone responses to standing after HDBR than males. Cardiovascular responses to standing before and after bedrest differed markedly: arterial pressure and heart rates increased with standing before HDBR, by contrast, arterial pressure decreased, with greater increases in heart rates after HDBR. In both sexes, all hormonal responses to standing were greater after HDBR. The results show clearly that similar responses to standing as well as to HDBR occur in both sexes, but that females exhibit greater PRA and aldosterone responses than males.

Introduction

Both males and females serve as astronauts, and thus, are exposed to the weightlessness of microgravity during space flight. In microgravity, the reduction of the influence of gravitational forces by directional changes in posture, or reducing their effects on the ground by immersion, trigger shifts in body fluids (refs. 1-3). Under these conditions, central vascular receptors perceive the translocation of fluid from the extremities to the chest and head as an increase in total blood volume. As the Henry-Gauer hypothesis proposes (ref. 4), such stimulation of volume or baroreceptors leads to increased water and sodium (Na) excretion, and is accompanied, and presumably mediated, by immediate reductions in circulating plasma renin activity (PRA), vasopressin (AVP), aldosterone (ALDO) (refs. 5 and 6) and an increase in atrial natriuretic peptide (refs. 7 and 8).

Ground-based models for weightlessness in space include total body immersion (ref. 1) and head down bed rest (HDBR) (ref. 9). In a previous study of HDBR, we reported the acute endocrine and metabolic responses to the head down posture, and also found that the relationship between renin and aldosterone changed over the course of the following 6 days in HDBR. The altered relationship was not ascribable to changes in any variable that was known to affect aldosterone secretion directly (ref. 9). However, in that study, provocative tests of intravenous ACTH and saline infusions were given which may have interfered with the normal course of the responses in hormones, fluid, and electrolyte balance. For this reason it was important to determine the effects of –6° antiorthostatic bedrest (HDBR) in a study uninterrupted by such tests. In addition, very few bedrest studies have involved female subjects (e.g., refs. 10 and 11) and none have used the head down position to compare endocrine and electrolyte responses with those of males.

In this study, therefore, we compared the changes in the endocrine mechanisms regulating fluid and electrolyte balance during 7 days of HDBR in healthy male and

*Life Science Division, NASA Ames Research Center, Moffett Field, CA 94035-1000.

**UCSF, Department of Physiology, San Francisco, CA 94143.

†Biomedical Operations, NASA Kennedy Space Center, FL 32899.

female subjects. To determine whether HDBR differentially affected subsequent responses to provocative stimuli, we also compared the cardiovascular and endocrine responses to quiet standing for 2 hours prior to, and immediately after HDBR.

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Methods

Subjects

Eight male (35-50 years old) and eight pre-menopausal female (30-45 years old) volunteers participated in the study (table 1). Subjects were selected following physical and psychological examinations from groups of 14 to 16 and were in excellent health with no history of chronic or recent acute illness. In order to reduce potential variability, female subjects were selected to participate in the study during the first two weeks of their menstrual cycle. Two female subjects had had hysterectomies. Subjects of both sexes were selected to cover the widest possible range of "normal" blood pressures and plasma volumes, so that a fair assessment of the contribution of their initial physiological state to the response to bedrest could be made. The study plan was approved by the NASA Ames Research Center Human Experiments Review Board. Subjects were thoroughly briefed about the experimental procedures and informed written consent was obtained. No medications, including oral contraceptives, smoking or caffeine-containing drinks were allowed during the study.

Experimental Procedures

Subjects remained in the Human Research Facility (HRF) of the Ames Research Center for a total of 14 days, including 5 ambulatory control days, 7 days of HDBR and 2 days of post-bedrest recovery. A diet of 120-140 mEq Na/day and 60-80 mEq K/day was used throughout the study. Fluid intake was also measured and controlled, not to exceed 1.5 L/day. Total caloric intake ranged from 2200-2500 calories/day for the males and 1800-2300 calories/day for the females. Twenty-four hour urine collections were made throughout the study. Plasma volume (PV) was determined on day 3 of the ambulatory control period preceding bedrest and again on the third day after HDBR began. A modified Evans blue dye dilution method was used to measure PV (refs. 12 and 13). Single, fasting, early morning blood samples were also taken at intervals during the study. Systolic and diastolic blood pressure and pulse rate were measured 4 times daily (0800, 1200, 1600, 2000).

Head Down Bedrest

During the head down bedrest period, subjects were allowed to lie on their sides, prone, or supine. They were also allowed one pillow but were asked to keep it flat. At mealtime, the subjects were allowed to prop themselves on an elbow. Their feet were higher than their heads at all times. Although the subjects' appetites generally decreased during the head down period compared to control, they were urged to eat and did eat all meals completely during the study. Any uneaten food was measured and the information incorporated in the balance data.

During the control, pre-bedrest period, subjects were encouraged to be active. A questionnaire, administered during the selection phase and designed to assess each individual's normal level of activity, was used to develop a mild activity regime for each subject during the ambulatory pre-bedrest control period. Subjects exercised on a bicycle ergometer 3 times/day for 10-min each, at a work intensity that produced a heart rate of 110-115 beats/min. This heart rate was equivalent to approximately 40% of the subject's age-predicted maximal heart rate and was designed to avoid sweating. Previous studies, using individuals confined to the HRF, who were ambulatory but necessarily less active, showed a tendency to develop cardiovascular deconditioning and associated endocrine and autonomic changes although to a much lesser extent than those in bedrest. We, therefore, found maintenance of activity in preventing such a deconditioning trend during the pre-bedrest ambulatory control period of the study to be extremely important.

Orthostatic Tests

Prior to the beginning of the study, a standard posture test was conducted to evaluate the subjects' responses to orthostatic challenge. This involved lying supine for one hour, followed by quiet standing, unsupported, for two hours. A sterile butterfly catheter was inserted in a peripheral vein at T-30 for the withdrawal of repeated blood samples. It was kept patent by a very slow drip of sterile 5% dextrose. The total volume of the drip was included in the daily fluid intake calculations and did not exceed 20ml. Blood pressure and heart rate were measured manually from the other arm. Blood samples were drawn at T-15 and immediately before standing (0), and at 5, 15, 30, 60 and 120 minutes after standing. They were used for the determination of PRA, ALDO, AVP, ACTH, and

cortisol. At the end of the 7-day HDBR period, similar measurements were made while subjects stood again unsupported for two hours. Both pre and post bedrest stand tests were conducted between 0800 and 1200 hr.

Blood and Urine Analyses

Individual urine voids were measured for volume, specific gravity and pH, and tested for the presence of glucose and protein. Aliquots of the pooled 24-hr urine were used for the determination of Na and K, cortisol, and ALDO. Control blood samples were taken in the sitting position (i.e., subject sitting on bed) before going head-down. Blood samples were analyzed for the determination of Na and K by flame photometry, and radioimmunoassay kits were used to measure cortisol (Diagnostic Products, Los Angeles, CA) and ALDO (Diagnostic Products kit, Coat-A-Count, Los Angeles, CA). Radio-immunoassay methods were also used to measure angiotensin-II (A-II) (ref. 14), AVP (ref. 15), ACTH (ref. 16) and PRA was estimated with a radioimmunoassay for angiotensin-I (A-I) (New England Nuclear, Boston, MA). Plasma estrogen and progesterone, and testosterone were also measured with radioimmunoassay kits in female and male subjects, respectively.

Statistical Analyses

The significance of hormone and electrolyte responses to postural change (control vs. head down) and gender differences was estimated by 1- and 2-way analysis of variance (ANOVA) corrected for repeated measures in 1 or 2 dimensions, and by paired t-tests. Post-hoc tests on significance of individual points were performed using Newman-Keuls tests. Three-way ANOVA (pre- post, gender, time after standing) was used to determine significance of differences between pre- and post- HDBR standing test.

Results

Seven Days Head Down Bedrest: Changes in Fluid and Electrolyte Balance

Figures 1, 2, and 3 compare the effect of 7 days head down bedrest on fluid, Na and K balance in male and female subjects. During the control period there was a consistent, positive balance between dietary intake and urinary excretion of fluid, Na and K. For both males and females, a significant change in fluid balance (fig. 1) in response to bedrest was observed, where the greatest diuresis was evident on the first day of bedrest ($P < 0.01$). The effect was transient and lasted two to three days. Upon re-ambulation, a marked, but not significant, fluid retention was seen ($P > 0.05$). These changes in fluid balance during HDBR were paralleled by a decrease in plasma (males 3.5%; females 8.1%, $P < 0.05$) and blood (males 2.9%; females 7.8%, $P < 0.05$) volume, measured on day 3 of bedrest (table 1).

Similar significant changes were observed in the excretion of Na (fig. 2) for both groups. The first few days of bedrest were characterized by a substantial negative Na balance ($P < 0.01$) which had recovered by the 5th and 3rd day of bedrest in males and females, respectively. On becoming ambulatory again there was significant Na retention in both groups ($P < 0.05$). Little overall change in K excretion was evident during these same first days of bedrest (fig. 3), so the net effect of bedrest was a marked increase in the urinary Na/K ratio in both sexes (fig. 4) on bedrest days 1 and 2 ($P < 0.05$); and a marked decrease in this ratio in response to re-ambulation ($P < 0.05$). Plasma Na, K, and protein remained unchanged throughout the study, but females had significantly ($P < 0.001$) lower circulating Na concentrations than males (table 2).

Seven Days HDBR: Hormonal Responses

Seven days of HDBR produced remarkably little effect on the plasma levels of Na, K, AVP, ACTH, or cortisol in either group when compared to the ambulatory control levels in the same subjects. PRA increased (fig. 5) during the 7 days of bedrest in the females only ($P < 0.01$). However, in this group neither plasma ALDO nor blood pressure were increased and, in fact, plasma ALDO decreased on the first day of bedrest ($P < 0.05$), thus becoming uncoupled from PRA (fig. 5). Similar uncoupling was seen on the first day of bedrest in the males. PRA was never significantly increased or decreased in this group, while plasma ALDO decreased ($P < 0.01$), suggesting a similar shift in the relationship between PRA and plasma ALDO in both groups during bedrest. Urinary ALDO showed similar patterns in both groups, with a very large increase in excretion in response to re-ambulation (fig. 5). The changes in plasma A-II on the third day of bedrest (not shown) closely paralleled those in PRA. The inverse relationship of urinary aldosterone excretion to the urinary Na/K ratio (fig. 6) during the HDBR period illustrates the consistent action of plasma ALDO on Na excretion throughout the study.

Plasma ACTH levels were significantly lower in females than in males ($P < 0.01$) at all time points tested, although plasma cortisol levels were no different (fig. 7). Urinary cortisol, however, was different between genders, with females showing lower urinary cortisol excretion than males throughout the bedrest period ($P < 0.05$) (fig. 7).

Although both groups showed marked increases in cortisol excretion on the first day of admission (from a baseline of approximately 50 μg/24 hr to 80.5 ± 6.8 μg/24 hr in males and 89.3 ± 26.8 μg/24 hr in females), only males responded with a similar increase on the first day of bedrest (111 ± 28.9 μg/24 hr in males and 41.0 ± 7.2 μg/24 hr in females). A slight decrease in plasma testosterone was observed on BR day 2 ($P = 0.051$) and recovered by BR day 3 (preBR control: 6.28 ± 0.62; BR2: 4.92 ± 0.44; BR3: 5.62 ± 0.40; BR5: 6.4 ± 0.63; BR7: 5.42 ± 0.46 ng/ml). The course of expected cyclic changes in plasma estrogen (C3: 114 ± 20; BR1: 132 ± 38; R + 1: 187 ± 82 pg/ml) and progesterone (C3: 2.7 ± 2.3; BR1: 2.3 ± 1.8; R + 1: 5.3 ± 2.2 ng/ml) associated with the menstrual cycle appeared unaffected by the 7 days of bedrest.

Responses to Standing Before and After HDBR

Figures 8 and 9 show, respectively, the cardiovascular and endocrine responses to quiet standing for 2 hours after lying down for one hour prior to bed rest (left panels) and after getting up from head down bedrest (right panels). All cardiovascular (fig. 8) and endocrine (fig. 9) responses to the two standing tests were highly significantly different ($p < 0.005$). Before HDBR, mean blood pressure and heart rate increased; however, there were significant sex differences in systolic and pulse pressures. Females had lower systolic pressure ($p = 0.012$) and did not increase pulse pressure or mean arterial pressure as did males on standing ($p = 0.03$). Standing after bed rest caused a precipitous decrease in mean arterial pressure; initially and after standing, systolic and diastolic pressures were both significantly lower in women than men ($p = 0.024$ and 0.037, respectively), although pulse pressure narrowed, and heart rate increased similarly in both sexes. Although there were sex differences in the PRA and ALDO responses to standing before bed rest ($p = 0.001$ and 0.004, respectively), there was no sex difference in the PRA response to standing after HDBR. However, the larger ALDO response to standing was maintained in the females ($p < 0.001$). There was a sex x time interaction in ALDO ($p = 0.002$) and ACTH ($p = 0.001$) responses to standing; females reached peak responses more slowly than males.

Discussion

Our data indicate that females and males show similar metabolic and endocrine responses to HDBR. There are clear, but minor, sex differences in both the responses to head down bed rest and to the cardiovascular challenge of standing both before, and after HDBR. The differences reside primarily in responses of the PRA - ALDO system to the various stimuli applied. Females had larger PRA and ALDO responses to standing before bed rest, and during bed rest they tended to maintain PRA and ALDO at elevated levels. By contrast, males had small PRA and ALDO responses to standing before bed rest, and tended to maintain the decreases in PRA and ALDO that occurred during the first day of bed rest. Standing at the end of HDBR resulted in similar PRA responses in males and females; however, the greater responsiveness in ALDO was maintained in the females.

The sex differences in responses of the renin-angiotensin system observed in this study may be a consequence of the possibility that the females adjusted their extracellular volumes downward during the dietary equilibration, ambulatory portion of the study. During this period there was little change in fluid and Na^+ balance in the male subjects, but there was a less positive fluid and Na^+ balance in the females during the 4th and 5th days before HDBR, suggesting that there may have been a reduction of extracellular volume. This was followed in the females by a greater loss of plasma and blood volume measured on day 3 of HDBR, and accompanied by sustained secretion of PRA and ALDO. The decrease in plasma and blood volume observed in the males of this study was unusually small. Generally, decreases in volume averaging 10% are observed in males (refs. 9, 13, and 17), similar to the average decreases of the females in this study.

A second sex difference which emerged from the study involved the pituitary-adrenal axis. Basal AM plasma ACTH levels were consistently lower in females than males, although plasma cortisol concentrations did not differ. Furthermore, urinary cortisol concentrations were increased above the mean obtained during the ambulatory period in males and decreased in females. Both groups returned to their pre-bedrest urinary cortisol levels upon resuming upright posture and reambulating. Since early morning plasma cortisol values did not reflect the sex differences seen in 24 hour urinary cortisol excretion, the primary source for the increased excretion in the males may be cortisol secretion during the evening. Previous observations in females on a 14 day, horizontal, bedrest study showed a reduction in amplitude and in the mean daily plasma cortisol rhythm (ref. 18). Increased cortisol excretion in male subjects during horizontal bedrest has been consistently observed over the years (ref. 19), and traditionally has been attributed to bedrest. Our findings clearly show that this is not so. In reference 20, we reported the effects of 10 days horizontal bedrest in males and females aged 35-65 in which similar sex differences in cortisol excretion were observed during bedrest, i.e., an increase in males and a decrease in females. We propose that the perception of the bedrest situation, not bedrest itself, is the attributable factor for the observed sex

difference in cortisol excretion. In subsequent studies, we have been able to maintain normal cortisol excretion in males of the same age group, even over 30 days of HDBR (ref. 21) by mixing male subjects experienced with HDBR with naive individuals.

In these studies, again, there was a tendency for an altered relationship between PRA and ALDO during HDBR. After the first twenty-four hours of HDBR, plasma ALDO had decreased in spite of normal or elevated PRA levels. This was especially noticeable in the females, showing a sustained increase in PRA and a paradoxical decrease in ALDO. We reported this dissociation between PRA and plasma ALDO in similar HDBR studies over 7 days (ref. 9) as well as 30 days (ref. 21) in previous studies using male subjects. However, in the present study, although PRA levels were not elevated in the males, they still showed reduced plasma ALDO levels relative to PRA. Other factors measured, that are known to alter the plasma ALDO response to PRA that might explain this apparent uncoupling, such as ACTH or electrolytes, were unchanged. Since AII changes, measured on day 3 of HDBR, closely paralleled those in PRA, increased PRA levels in HDBR did not appear to be associated with a reduced ability to convert AI to AII, although we have found indirect evidence for such a defect in more prolonged HDBR exposures (ref. 21).

Plasma ALDO and twenty-four hour unrinary ALDO were closely, but inversely, related to the early increases and progressive decreases in urinary Na/K ratios. Natriuresis was evident in both sexes for at least the first three days of HDBR. Because of the noticeable absence of any sustained reduction of PRA or aldosterone during this time, other mechanisms must be involved in the apparent renal Na escape. Natriuretic peptides would appear to be the most likely candidates. The administration of αhANP in a bolus (ref. 22) or infused (ref. 23) induce major increases in sodium excretion while suppressing the renin-angiotensin-aldosterone system. The suppression of aldosterone was particularly pronounced. However, PRA and plasma A-II were also reduced during the infusion of αhANP (ref. 23), although not to the same extent, allowing for the possibility that the inhibition of aldosterone was, in part, renin dependent. We have been unable to measure consistent increases in plasma ANP in response to going head down from the vertical in these and other subjects eating a diet containing 120mEq sodium per day. This is in agreement with Hollister et al. (ref. 24) who were also unable to show significant plasma ANP concentration changes in response to standing in subjects consuming 111mEq sodium, whereas increasing dietary sodium intake resulted in the expected ANP response to postural change. In other studies, we and others have measured significant increases in plasma ANP during these early phases of HDBR that would parallel the early natriuresis (ref. 25 and 8). However, time courses of changes in ANP reported by others still do not completely account for the long lasting natriuresis. In a 30 day HDBR study, we measured significant reductions in ANP after prolonged bedrest (unpublished observations). It is possible that under these circumstances, HDBR may either blunt renal responses to ANP or aldosterone (ref. 26 and 7), or disturb the normal nocturnal decrease in electrolyte excretion (ref. 27).

The effect of 7 days of HDBR on the cardiovascular responses to standing was expected and has been reported by others (ref. 3). This is the first report, of which we are aware, that compares endocrine responses to standing before and after bed rest of any sort. All measured hormonal responses to standing were significantly greater after HDBR. This is almost certainly a consequence of the altered cardiovascular dynamics observed after HDBR. Mean arterial pressure decreased slightly in females and increased slightly in males after standing prior to bedrest; by contrast, mean arterial pressure in both groups decreased with standing after HDBR. Before bedrest, diastolic blood pressure increased in males but not in females; and this response, coupled with increased heart rate and moderate endocrine responses, was adequate to maintain fairly stable mean arterial pressure. After HDBR, both systolic and diastolic blood pressures decreased with standing, despite marked increases in heart rate. This decrease in mean arterial pressure when added to the decreased plasma volume and the volume shifts that occur with standing would account for the marked augmentation in the hormonal responses observed after HDBR.

In summary, there were only minor gender differences in cardiovascular, metabolic, and endocrine responses to HDBR and quiet standing before and after HDBR. These consistently appeared in the PRA - ALDO system, and may be explained by the greater volume loss that occurred with HDBR in the female subjects in these studies. There were also differences in the pituitary-adrenal response to HDBR, in that, urinary cortisol excretion increased in males and decreased in females, possibly because there is a gender difference in the perception of the head-down stimulus. As in previous studies, there tended to be a dissociation between PRA and ALDO during HDBR which is not explained by known regulators of this system. Finally, there were marked differences in cardiovascular and endocrine responses to standing before and after HDBR. The marked increases in hormonal responses are probably accounted for by the loss of blood volume that occurs during HDBR and the decrease in mean arterial pressure that occurs after, but not before, HDBR.

References

1. Epstein, M.: Renal Effect of Head-Out Water Immersion in Humans: A 15-Year Update. Physiol. Rev., vol. 72, 1992, pp. 563-621.

2. Leach, C. S.: An Overview of the Endocrine and Metabolic Changes in Manned Spaceflight. Acta Astronautica, vol. 8, 1981, pp. 977-986.

3. Nixon, J. V.; Murray, R. G.; Bryant, C.; Johnson, R. L.; Mitchell, J. H.; Holland, O. B.; Gomez-Sanchez, C.; Vergne-Marini, P.; and Blomqvist, G.: Early Cardiovascular Adaptation to Simulated Zero Gravity. J. Appl. Physiol., vol. 46, 1979, pp. 541-548.

4. Gauer, H.; and Henry, J.: Circulatory Basis of Fluid Volume Control. Physiol. Rev., vol. 43, 1963, pp. 423-481.

5. Convertino, V. A.; Thompson, C. A.; Benjamin, B. A.; Keil, L. C.; Savin, W. M.; Gordon, E. P.; Haskell, W. L.; Schroeder, J. S.; and Sandler, H.: Hemodynamic and ADH Responses to Central Blood Volume Shifts in Cardiac-Denervated Humans. Clin. Physiol., vol. 10, 1990, pp. 55-67.

6. Henry, J. P.; Gauer, O. H.; and Reeves, J. L.: Evidence of the Atrial Location of Receptors Influencing Urine Flow. Circ. Res., vol. 4, 1956, pp. 85-90.

7. Shiraki, K.; Konda, N.; Sagawa, S.; Claybaugh, T. R.; and Hong, S. K.: Cardiorenal-Endocrine Responses to Head-Out Immersion at Night. J. Appl. Physiol., vol. 60, 1986, pp. 176-183.

8. Wade, C. E.; Vernikos, J.; Evans, J.; and O'Hara, D.: Periodic Upright Posture Negates the Suppression of Neuroendocrine Responses to Head Down Bedrest. Aviat. Space Environ. Med., vol. 63, 1992, p. A65.

9. Dallman, M. F.; Vernikos, J.; Keil, L. C.; O'Hara, D.; and Convertino, V.: Hormonal, Fluid and Electrolyte Responses to 6° Anti-Orthostatic Bed Rest in Healthy Male Subjects. In: Catecholamines and Stress: Volume 4, edited by R. Kvetnansky and E. Usdin. New York: Gordon and Breech, 1984, pp. 1054-1077.

10. Convertino, V. A.; Goldwater, D. J.; and Sandler, H.: Bedrest-Induced Peak VO_2 Reduction Associated with Age, Gender and Aerobic Capacity. Aviat. Space Environ. Med., vol. 57, 1986, pp. 17-22.

11. Convertino, V. A.; Stremel, R. W.; Bernauer, E. M.; and Greenleaf, J. E.: Cardiorespiratory Responses to Exercise after Bedrest in Men and Women. Acta Astronautica., vol. 4, 1977, pp. 895-905.

12. Greenleaf, J. E.; Convertino, V. A.; and Margseth, G. R.: Plasma Volume during Stress in Man: Osmolality and Red Cell Volume. J. Appl. Physiol., vol. 47, 1979, pp. 1031-1038.

13. Greenleaf, J. E.; Vernikos, J.; Wade, C. E.; and Barnes, P. R.: Effect of Leg Exercise Training on Vascular Volumes during 30 Days Head Down Bedrest. J. Appl. Physiol., vol. 72, 1992, pp. 1887-1894.

14. Matsukawa, S.; Keil, L. C.; and Reid, I. A.: Role of Endogenous Angiotensin-II in the Control of Vasopressin Secretion during Hypovolemia and Hypotension in Conscious Rabbits. Endocrinology, vol. 128, 1991, pp. 204-210.

15. Keil, L. C.; and Severs, W. B.: Reduction in Plasma Vasopressin Levels of Dehydrated Rats Following Acute Stress. Endocrinology, vol. 100, 1977, pp. 30-38.

16. Wood, C. E.; Shinsako, J.; and Dallman, M. F.: Comparison of Canine Responses to Mean and Phasic Increases in ACTH. Amer. J. Phys., vol. 242, 1982, pp. E102-E108.

17. Heer, M.; Drummer, C.; Baisch, F.; Maass, H.; Gerzer, R.; Kropp, J.; and Blomquist, C. G.: Effects of HDT and Saline Loading on Body Weight, Fluid and Electrolyte Homeostasis in Man. Acta Physiol. Scand., vol. 144, no. S604, 1992, pp. 13-22.

18. Vernikos-Danellis, J.; Dallman, M. F.; Forsham, P.; Goodwin, A. L.; and Leach, C. S.: Hormonal Indices of Tolerance to +Gz Acceleration in Female Subjects. Aviat. Space Environ. Med., vol. 49, 1978, pp. 886-889.

19. Leach, C. S.; Hulley, S. B.; Rambaut, P. C.; and Dietlein, L. F.: The Effect of Bedrest on Adrenal Function. Space Life Sci., vol. 4, 1973, pp. 415-423.

20. LaRochelle, F.; Leach, C. S.; and Vernikos-Danellis, J.: Effects of Age and Sex on Hormonal Responses to Weightlessness Simulation. The Physiologist, vol. 25, 1982, pp. 304-305.

21. DeCherney, G. S.; Dallman, M. F.; Van Loon, G.; Keil, L. C.; Convertino, V. A.; O'Hara, D.; and Vernikos-Danellis, J.: Simulation Weightlessness: Hormonal, Fluid and Electrolyte Consequenses of 30 days –6° Headdown Bedrest. Proc. Endocrine Soc., 1989, p. 466.

22. Richards, A. M.; Nicholls, M. G.; Ikram, H.; Webster, M. W. I.; Yandle, T. G.; and Espiner, E. A.: Renal, Hemodynamic and Hormonal Effects of Human Alpha Atrial Natriuretic Peptide in Healthy Volunteers. Lancet., vol. 1, 1985, p. 545.

23. Cuneo, R. C.; Espiner, E. A.; Nicholls, M. G.; Yandle, T. G.; Joyce, S. L.; and Gilchrist, N. L.: Renal, Hemodynamic, and Hormonal Reponses to Atrial Natriuretic Peptide Infusions in Normal Man, and Effect of Sodium Intake. JCEM., vol. 63, 1986, pp. 946-953.

24. Hollister, A. S.; Tanaka, I.; Imada, T.; Onrot, J.; Biaggioni, I.; Robertson, D.; and Inagami, I.: Modulation of Plasma Atrial Natriuretic Factor Levels in Human Subjects by Sodium Loading and Posture Change. Hypertension, vol. 8, 1986, pp. 106-111.

25. Gauquelin, G.; Allevard, A. M.; Güell, A.; Vorobiev, D.; Grigoriev, A. I.; and Gharib, C.: Presence of Atrial Natriuretic Factor in Saliva: Comparison of Plasma and Salivary Concentrations during a Head Down Tilt. Physiologist., vol. 35 (Suppl.), no. S190-S191, 1992.

26. Miki, K.; Shiraki, K.; Sagawa, S.; DeBold, A. J.; and Ki Hong, S.: Atrial Natriuretic Factor during Head-Out Immersion at Night. Am. J. Physiol., vol. 254, 1988, pp. R235-241.

27. Minors, D. S.; and Waterhouse, J. M.: Circadian Rhythms of Urinary Excretion: The Relationship between the Amount Excreted and Circadian Changes. J. Physiol. (Lond.)., vol. 327, 1982, pp. 39-51.

Table 1. Subject descriptive data and blood and plasma volumes before and during bedrest

	Age (yr)	Height (cm)	Weight (kg)	Control Plasma volume (ml)	Control Plasma volume (ml/kg)	Control Blood volume (ml)	Control Blood volume (ml/kg)	Bedrest day 3 Plasma volume (ml)	Bedrest day 3 Plasma volume (ml/kg)	Bedrest day 3 Blood volume (ml)	Bedrest day 3 Blood volume (ml/kg)
						Males					
Mean	46	181	84.0*	3679*	43.4	5968	70	3533*	41.9	5761	68
Se	1	1	1.3	108	0.8	170	1	78	0.4	139	1
						Females					
Mean	37	165	64.4*	2636*	42.0	4049	64	2404*	38.6†	3683	59
Se	1	1	1.3	26	0.9	42	1	25	0.8	38	1

Data are mean ± standard error (SE).
*Gender, $P < 0.005$.
†Bedrest, $P < 0.05$.

Table 2. Effect of 7 days of 6° head down bedrest (BR) on plasma sodium, potassium and protein concentrations and on body weight of male and female subjects. [C3, C5, and R + 1 denote ambulatory control and recovery days.]

		C3	C5	BR2	BR3	BR5	BR7	R + 1
Plasma sodium Eq/L	Males	141.66 ±2.05	141.57 ±1.42	138.99 ±0.66	139.94 ±0.37	139.94 ±0.39	141.50 ±1.77	140.31 ±0.47
	Females	138.13* ±0.72	136.14* ±1.26	136.38* ±0.86	136.38* ±0.26	137.25* ±0.59	136.63* ±0.63	135.75* ±0.94
Plasma potassium mEq/L	Males	4.20 ±0.18	4.24 ±0.08	4.09 ±0.10	4.13 ±0.09	4.29 ±0.15	4.40 ±0.14	4.48 ±0.11
	Females	4.29 ±0.13	4.18 ±0.11	3.96 ±0.09	4.23 ±0.09	4.41 ±0.81	4.23 ±0.12	4.14 ±0.15
Plasma protein gm/100ml	Males	7.13 ±0.11	7.43 ±0.28	7.16 ±0.12	7.23 ±0.15	7.40 ±0.11	7.41 ±0.14	7.59 ±0.13
	Females	7.11 ±0.16	7.26 ±0.13	7.18 ±0.16	6.93 ±0.22	7.14 ±0.19	7.29 ±0.20	7.28 ±0.13
Body weight kg	Males	83.2 ±4.5	83.0 ±4.3	83.2 ±4.3	82.9 ±4.3	82.7 ±4.1	82.5 ±4.1	82.8 ±4.0
	Females	64.4 ±4.3	64.5 ±4.3	64.1 ±4.1	63.8 ±4.2	64.0 ±4.3	63.8 ±4.4	64.2 ±4.3

*Gender, $P < 0.001$.

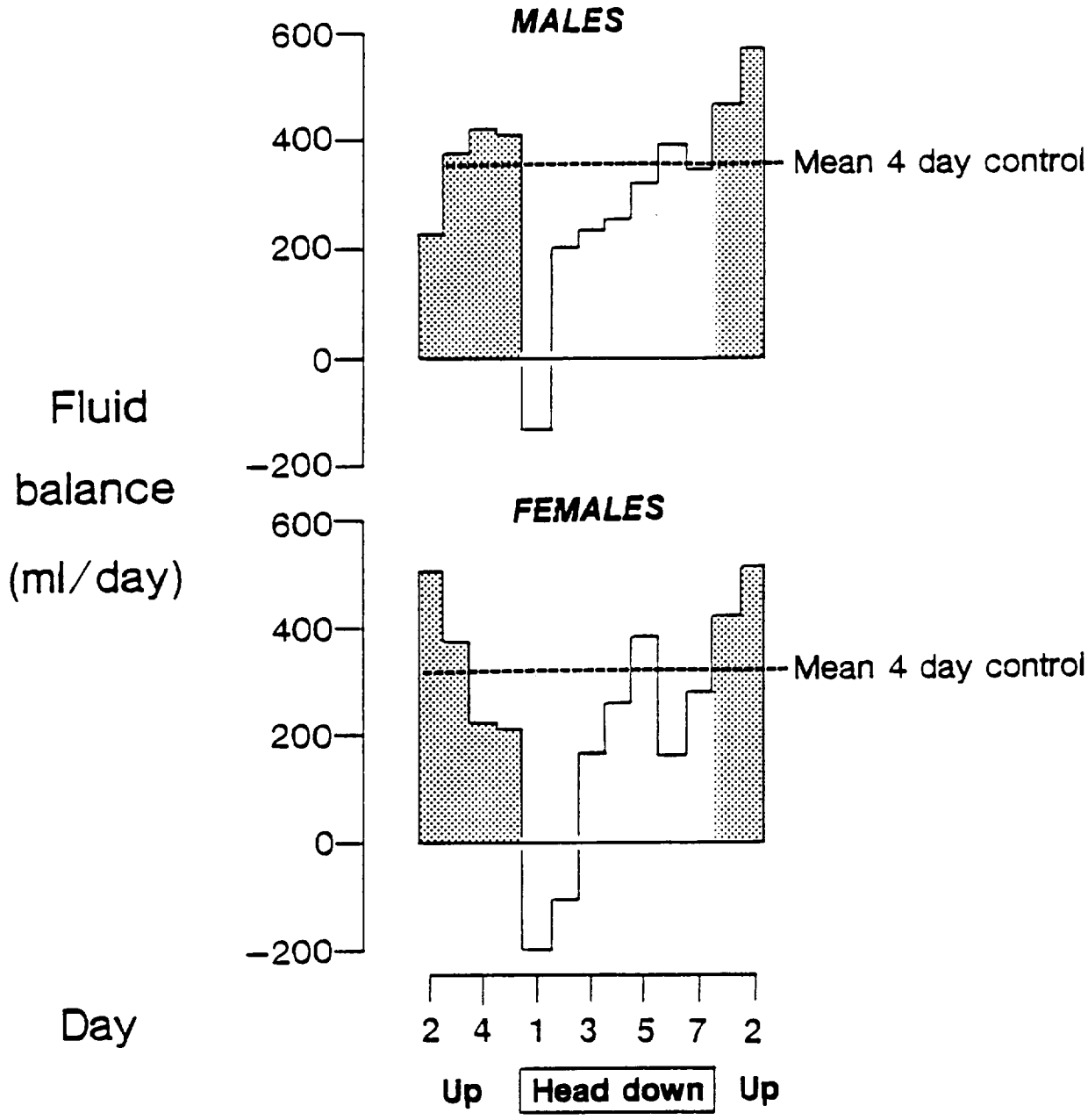

Figure 1. Daily fluid balance (intake-urine excretion) of male and female subjects before, during, and after 7 days of HDBR. HDBR began on day 6 of the study. Broken line is average of 4 control days immediately preceding HDBR. Stippled areas denote subjects were ambulatory. Significant diuresis ($P < 0.01$) on day 1 of HDBR in both sexes.

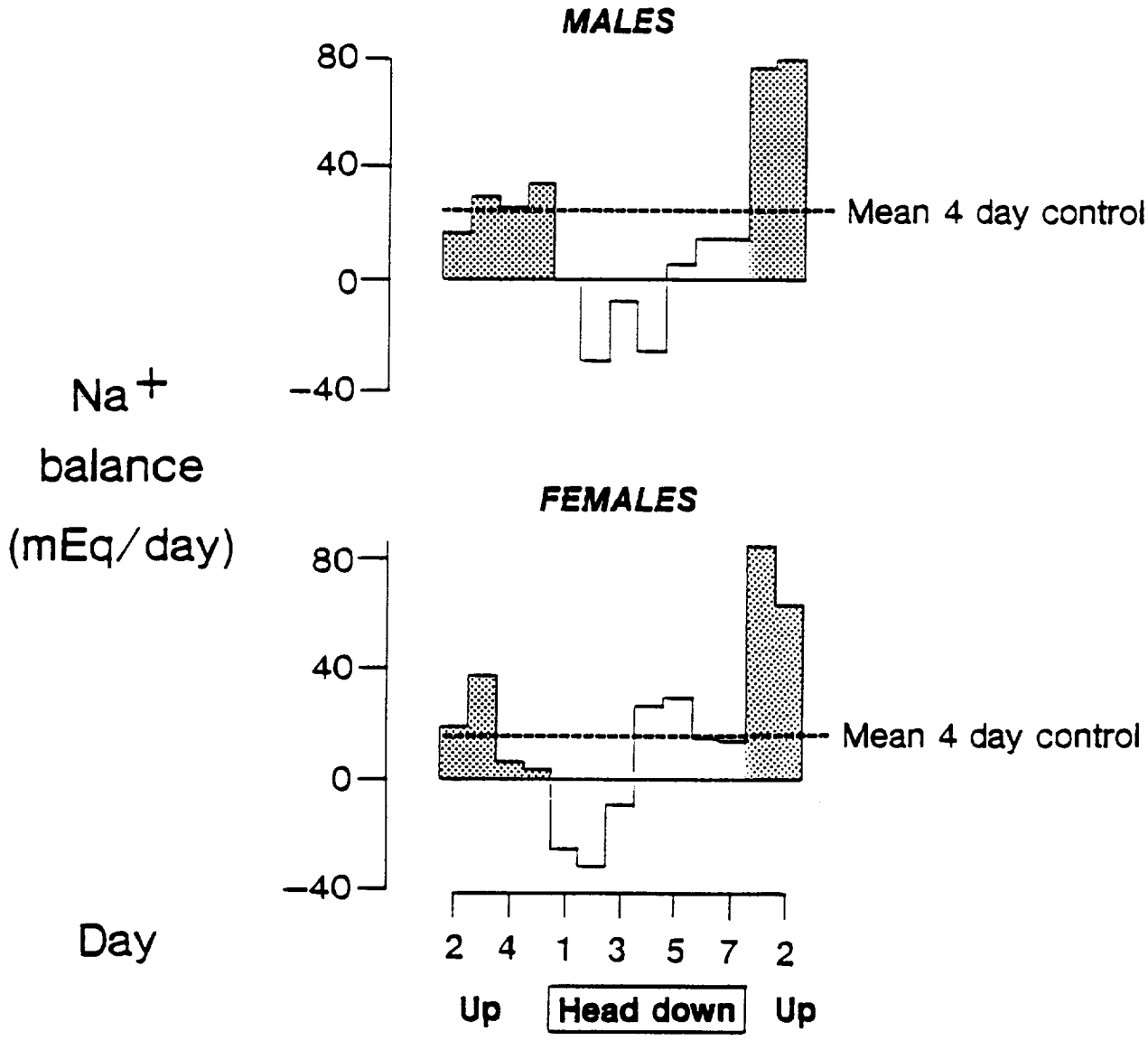

Figure 2. Daily sodium balance (intake-urinary excretion) in male and female subjects before, during, and after 7 days of -6° HDBR. HDBR began on day 6 of the study. Stippled areas denote subjects were ambulatory. Broken line is average of 4 control days immediately preceding HDBR. Sodium balance was significantly below control ($P < 0.01$) on days 1-3 during HDBR (in both sexes) and above control ($P < 0.05$) after HDBR.

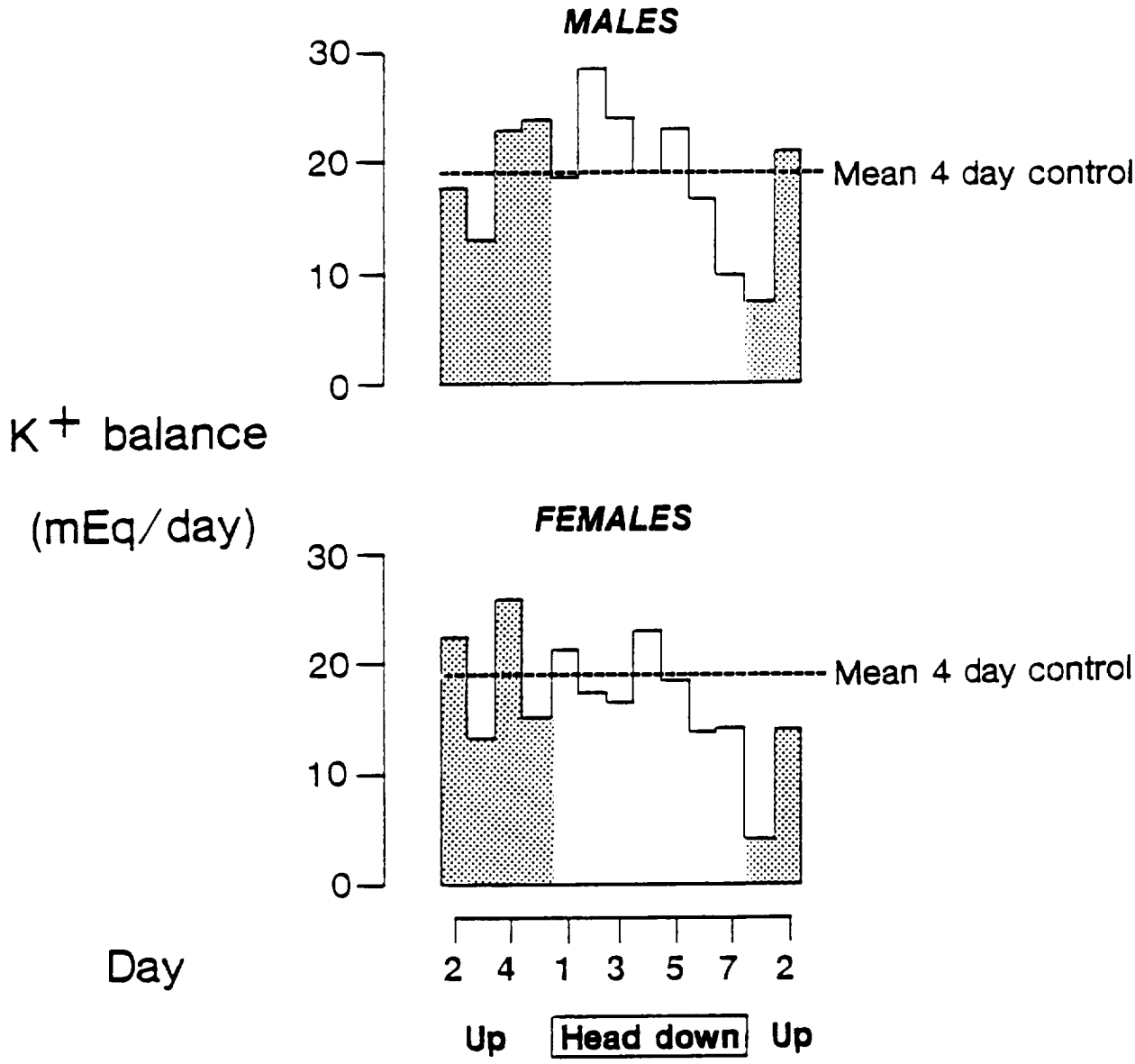

Figure 3. Daily potassium balance (intake-urinary excretion) in male and female subjects before, during, and after 7 days of -6° HDBR. HDBR began on day 6 of the study. Stippled areas denote subjects were ambulatory. Broken line is average of 4 control days immediately preceding HDBR. Significant kaliuresis ($P < 0.01$) in both sexes on first day after HDBR.

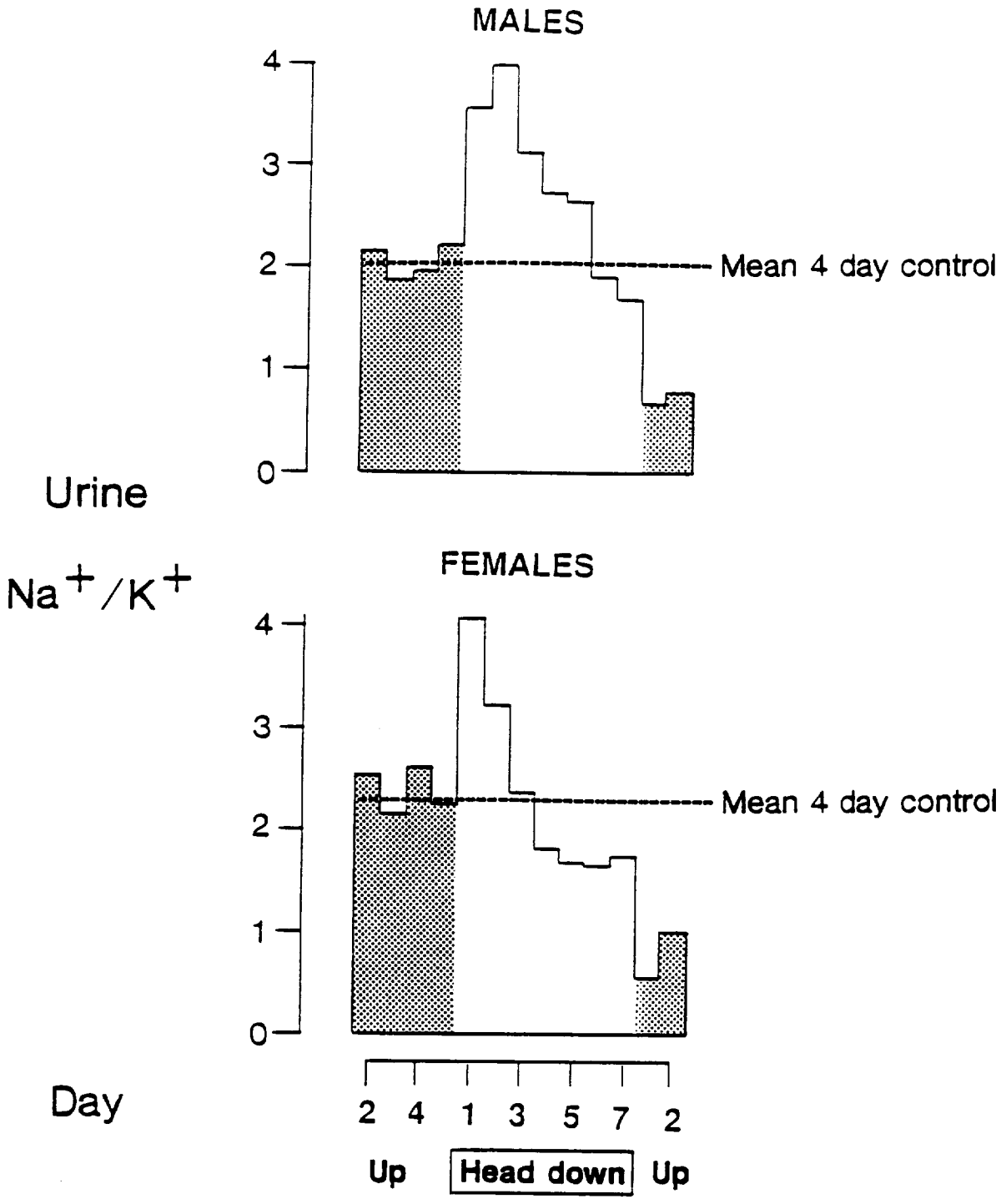

Figure 4. Twenty-four hour urinary sodium/potassium ratios in male and female subjects before, during, and after 7 days of HDBR. HDBR began on day 6 of the study. Stippled areas denote subjects were ambulatory. Broken line is average of 4 control days immediately preceding HDBR.

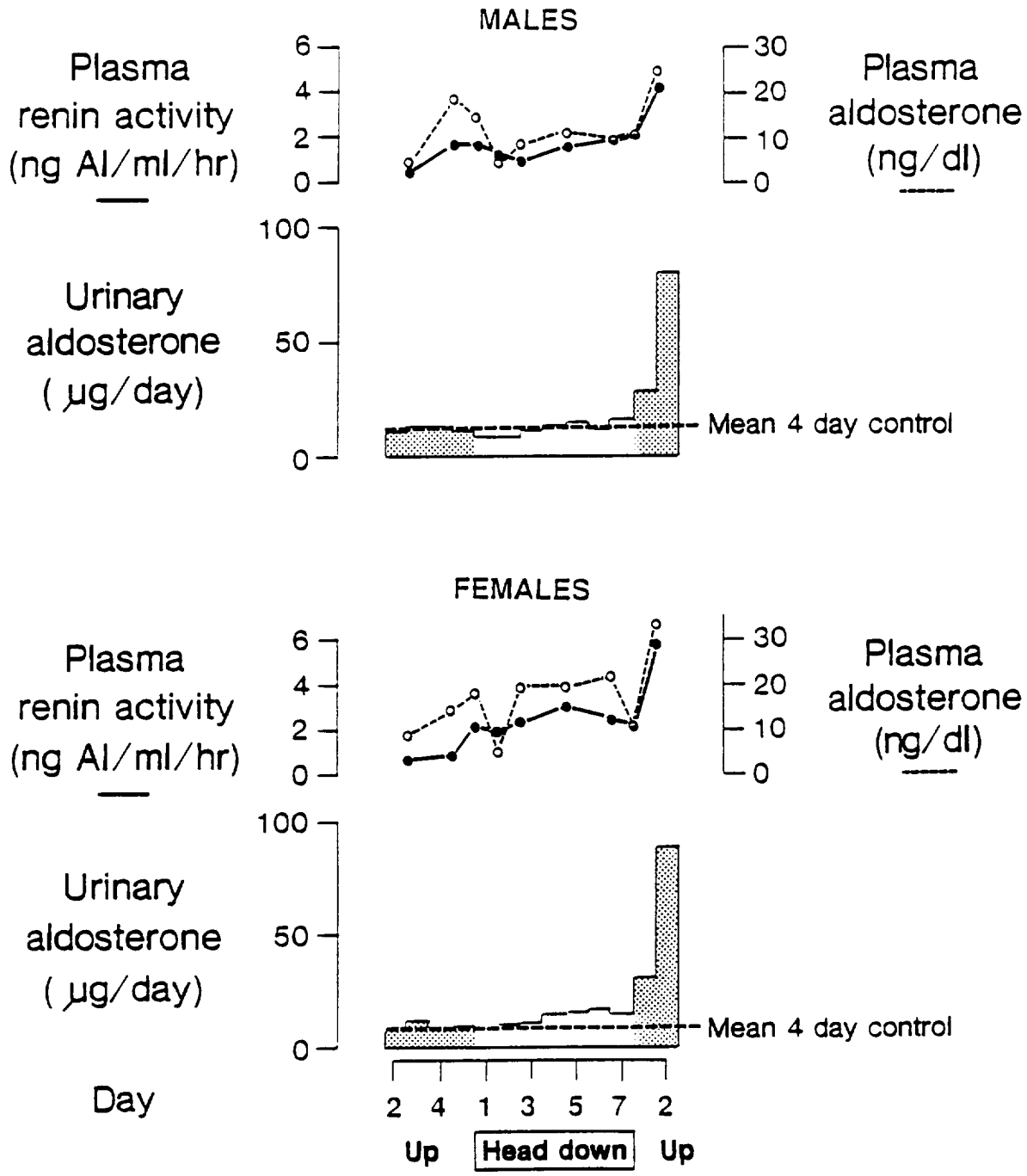

Figure 5. Plasma renin activity (PRA) and aldosterone (ALDO) in single early morning blood samples, and ALDO concentrations in 24 hr urine pools in male and female subjects before, during, and after 7 days of -6° HDBR. HDBR began on day 6 of the study. Stippled areas denote subjects were ambulatory. Broken line is average of 4 control days immediately preceding HDBR. (Standard error is not >34.40% of the mean for PRA, 19.2% for plasma ALDO and not >21.3% for urine ALDO.) PRA significantly increased ($P < 0.01$) in females only and plasma ALDO was significantly decreased ($P < 0.01$) in males only during HDBR. ALDO excretion significantly increased ($P < 0.01$) after HDBR only in both sexes.

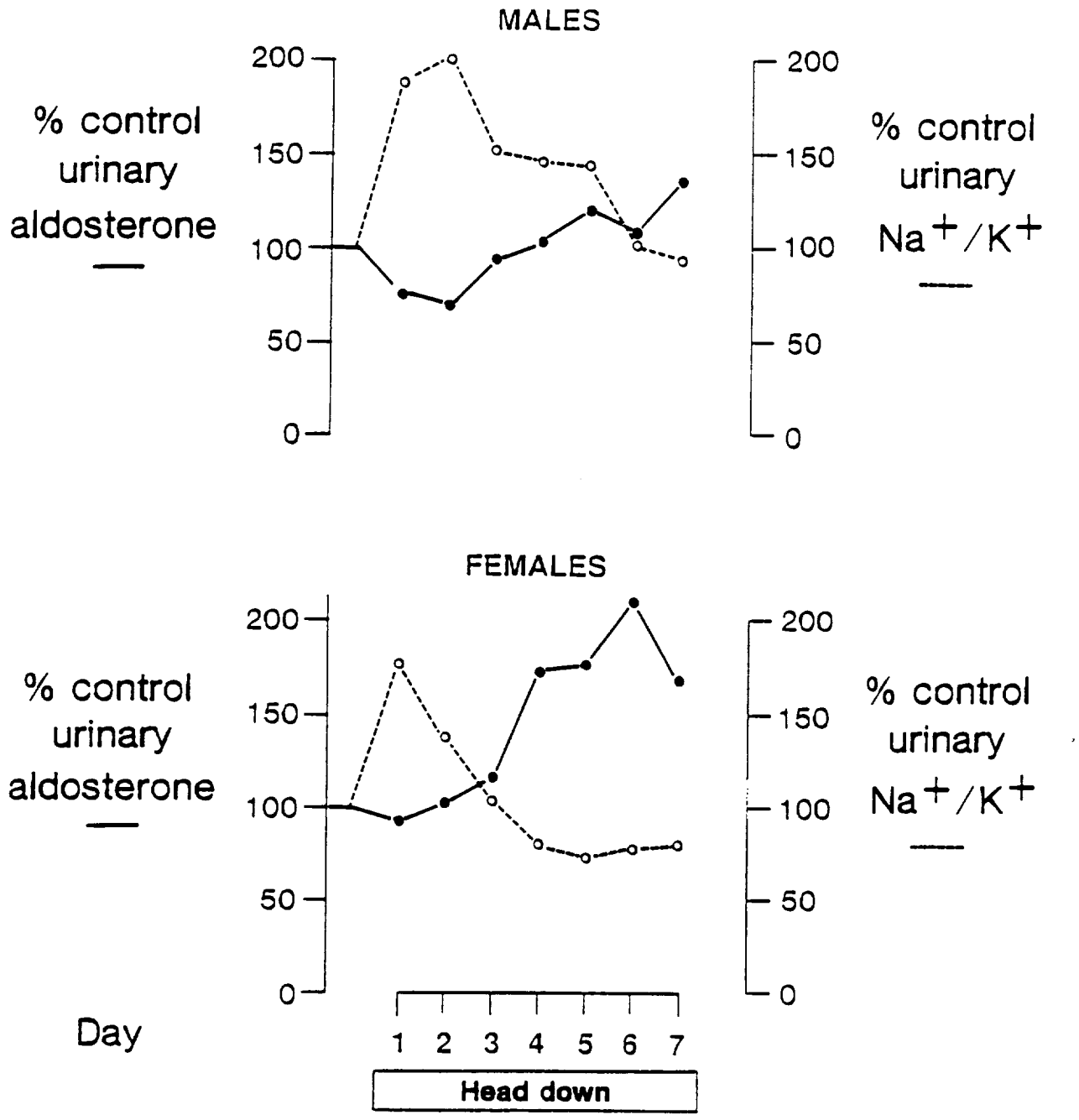

Figure 6. Relationship of the relative change in 24 hr urinary aldosterone to the sodium/potassium ratio in male and female subjects during 7 days of -6° HDBR; negative correlation (r = 0.269; slope = -3.78).

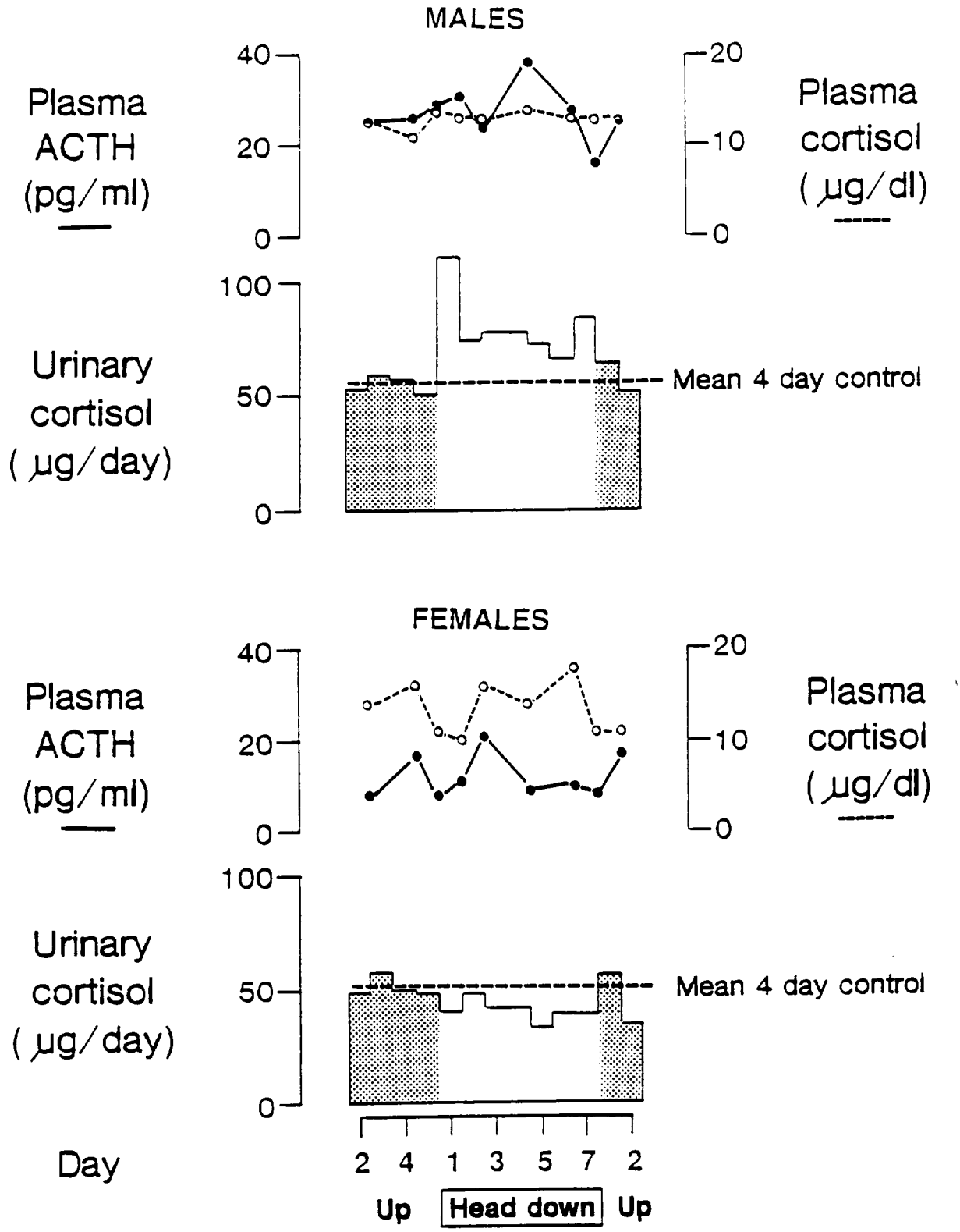

Figure 7. Plasma ACTH and cortisol concentrations in single early morning blood samples, and 24 hr urinary cortisol excretion in male and female subjects before, during, and after 7 days of -6° HDBR. HDBR began on day 6 of the study. Stippled areas denote subjects were ambulatory. Broken line is average of 4 control days immediately preceding HDBR. (Standard error is not >44.4% of the mean for plasma ACTH, 12.4% for plasma cortisol and 18.7% for urine cortisol). ACTH was significantly lower ($P < 0.01$) in females at all time points; cortisol excretion was also lower ($P < 0.05$) in females but higher ($P < 0.05$) in males during HDBR.

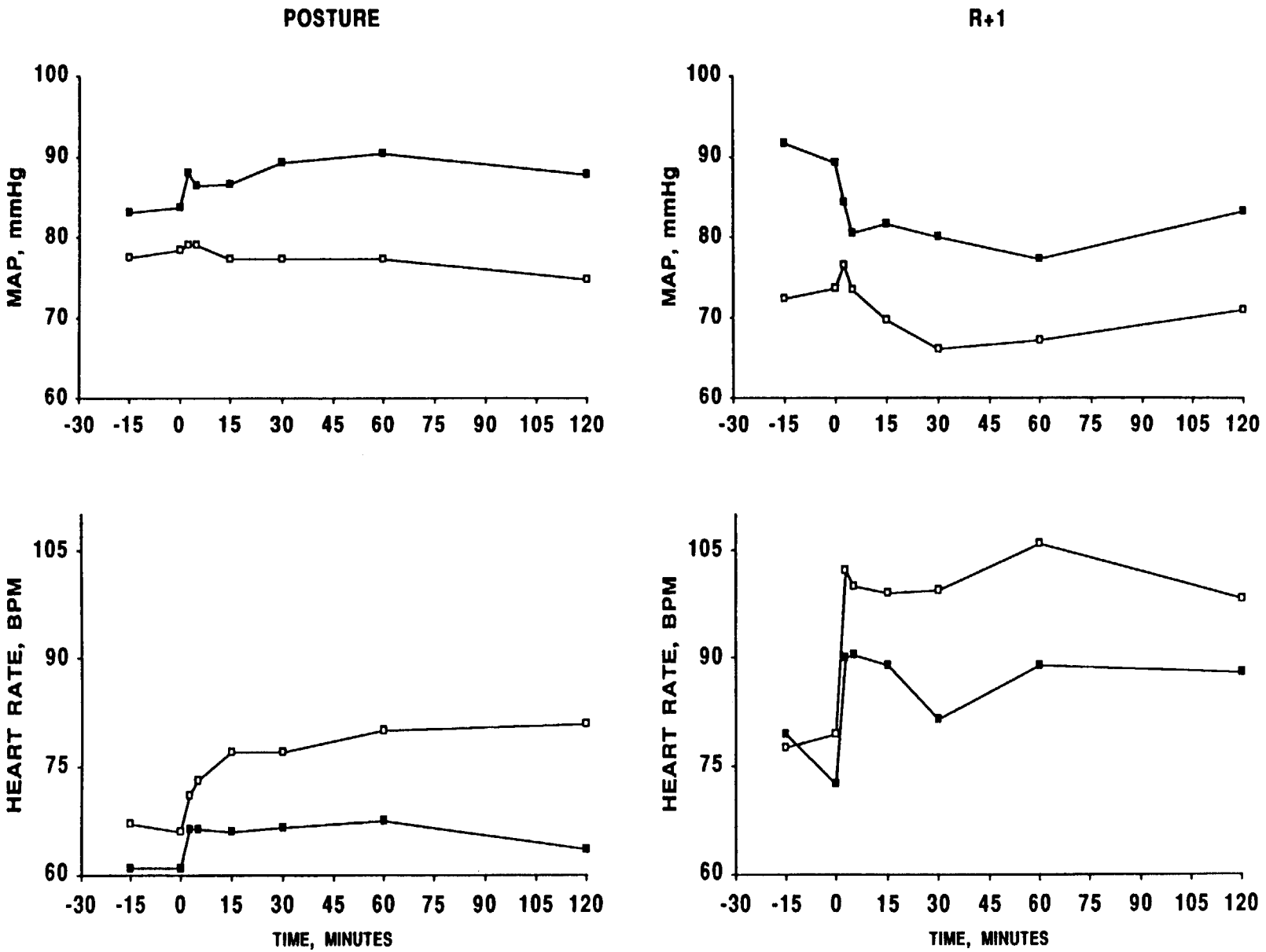

Figure 8. Mean arterial pressure (MAP) and heart rate (HR) responses to standing before (Posture) and after (R + 1) seven days of -6° head down bed rest, in male (black squares) and female (open squares) subjects. All subjects were supine for 1 hr before the Posture test. (Standard error is not >10% of the mean for heart rate and 9% of the mean for MAP.) HR response to standing was significantly greater ($P < 0.001$) after HDBR in both sexes. MAP increased significantly ($P < 0.01$) in males on standing before HDBR and decreased significantly ($P < 0.001$) after HDBR in both sexes.

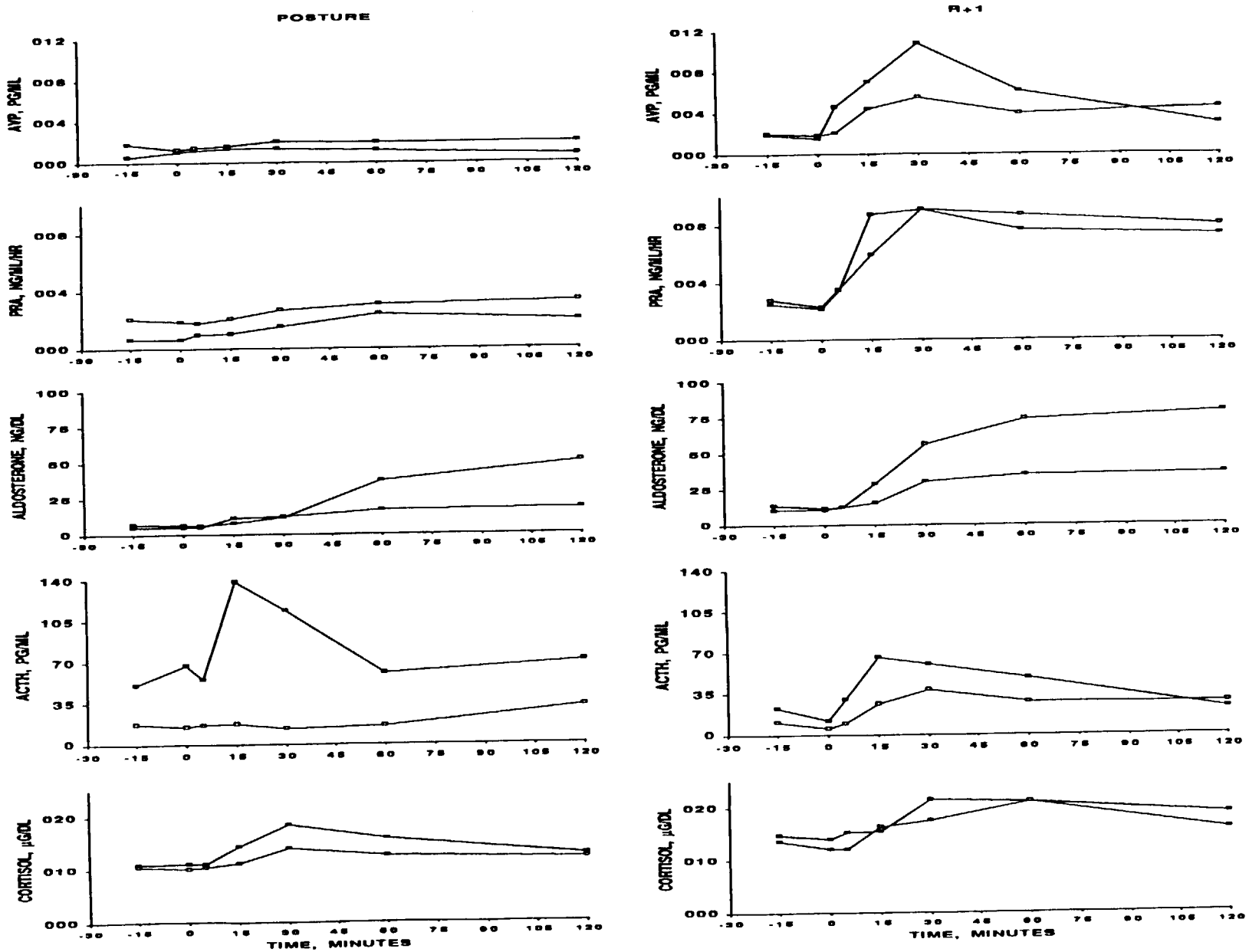

Figure 9. Circulating hormone responses to standing before (Posture) and after (R + 1) seven days of -6° head down bed rest, in male (black squares) and female (open squares) subjects. All subjects were supine for 1 hr before the Posture test. Female PRA response pre-bedrest and ALDO responses before and after HDBR significantly ($P < 0.001$) greater than males. PRA, ALDO and AVP significantly ($P < 0.003$) greater after HDBR in both sexes.

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J. Vernikos, M. F. Dallman,* L. C. Keil, D. O'Hara, and V. A. Convertino**

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Ames Research Center
Moffett Field, CA 94035-1000

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Point of Contact: J. Vernikos, Ames Research Center, MS 239-11, Moffett Field, CA 94035-1000
(415) 604-3736
*UCSF, Dept. of Physiology, San Francisco, CA **NASA Kennedy Space Center

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13. ABSTRACT ***(Maximum 200 words)***

Endocrine regulation of fluids and electrolytes during seven days of 6° head down bed rest (HDBR) was compared in male (n = 8) and, for the first time, female (n = 8) volunteers. The subjects' responses to quiet standing for 2 hr before and after HDBR were also tested. In both sexes, diuresis and natriuresis were evident during the first 2-3 days of HDBR, resulting in a marked increase in the urinary Na/K ratio and significant Na retention on reambulation. After the first day of HDBR, plasma renin activity (PRA) was increased relative to aldosterone, plasma volume was decreased and the renal response to aldosterone appeared to be appropriate. Circulating levels of arginine vasopressin (AVP), cortisol and ACTH were unchanged during HDBR. Plasma testosterone decreased slightly on day 2 of HDBR in males. The ratio of AM ACTH to cortisol was lower in females than in males because ACTH was lower in females. Urinary cortisol increased and remained elevated throughout the HDBR in males only. There were no gender differences in the responses to 7 day HDBR, except those in the pituitary-adrenal system; those differences appeared unrelated to the postural change. The provocative cardiovascular test of quiet standing before and after bed rest revealed both sex differences and effects of HDBR. There were significant sex differences in cardiovascular responses to standing, before and after HDBR. Females had greater PRA and aldosterone responses to standing before bedrest and larger aldosterone responses to standing after HDBR than males. Cardiovascular responses to standing before and after bedrest differed markedly: arterial pressure and heart rates increased with standing before HDBR, by contrast, arterial pressure decreased, with greater increases in heart rates after HDBR. In both sexes, all hormonal responses to standing were greater after HDBR. The results show clearly that similar responses to standing as well as to HDBR occur in both sexes, but that females exhibit greater PRA and aldosterone responses than males.

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